PATENT

Docket No. 4007528/173385

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/Holly D. Kozlowski/

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IN THE UNITED STATES PATENT & TRADEMARK OFFICE

Applicant:	Ulf Gyllensten et al	:	Confirmation No. 2553
Serial No.:	10/529,447	:	Group Art Unit: 1637
Filing Date:	December 12, 2005	:	Examiner: Thomas, David C.

For: **Method and Kit for Quantitative and Qualitative Determination of Human Papillomavirus**

APPEAL BRIEF

Mail Stop Appeal Brief - Patents
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Sir:

The present Appeal Brief is submitted in support of the Notice of Appeal filed electronically on March 26, 2009.

I. REAL PARTY IN INTEREST

The real party in interest for the present application is the Assignee of record, Cepheid, a California corporation having a place of business at 904 Caribbean Drive, Sunnyvale, California 94089.

II. RELATED APPEALS AND INTERFERENCES

No prior or pending appeals, interferences or judicial proceedings are know to the Appellants, the Appellants' undersigned legal representative, or the Assignee which may be related

to, directly affect or be directly affected by, or have a bearing on the Board's decision in the present appeal.

III. STATUS OF THE CLAIMS

Claims 1-8 and 15-17 have been cancelled from the present application. Claims 9-14 and 18-26 are pending and stand rejected, and are the subject of the present appeal. A complete copy of the appealed claims is set forth in the Claims Appendix.

IV. STATUS OF AMENDMENTS

No amendment was submitted subsequent to the final rejections set forth in the Official Action dated October 27, 2008.

V. SUMMARY OF THE CLAIMED INVENTION

The present invention is directed to kits for detection and quantification of human papillomavirus (HPV) (see the specification, page 1, Title at line 1 and the "Field of the Invention" section at lines 4-5).

According to independent claim 9, the kit for detection and quantification of HPV comprises a) the amplification primers SEQ ID NO: 1, SEQ ID NO: 2, SEQ ID NO: 3, SEQ ID NO: 4, SEQ ID NO: 5/SEQ ID NO: 6, SEQ ID NO: 7 and SEQ ID NO: 8, and the probes SEQ ID NO: 21, SEQ ID NO: 22 and SEQ ID NO: 23/SEQ ID NO: 24, for HPV 16, 31, 18, and 45 (see the specification, page 3, lines 29-32, and Tables 1 and 2 at pages 22 and 23, and see Tables 1 and 2 as amended in the Second Preliminary Amendment filed December 12, 2005 to include SEQ ID NOS). The kit of claim 9 optionally comprises b) the amplification primers SEQ ID NO: 9, SEQ ID NO: 10, SEQ ID NO: 11, SEQ ID NO: 12, SEQ ID NO: 13/SEQ ID NO: 14, SEQ ID NO: 15, SEQ ID NO: 16 and SEQ ID NO: 17/SEQ ID NO: 18 and the probes SEQ ID NO: 25, SEQ ID NO: 26 and SEQ ID NO: 27/SEQ ID NO: 28/SEQ ID NO: 29 for HPV 33, 35, 39, 52, and 58 (see the specification, page 3,

line 29-page 4, line 2, and Tables 1 and 2 at pages 22 and 23, and see Tables 1 and 2 as amended in the Second Preliminary Amendment filed December 12, 2005 to include SEQ ID NOS).

Claims 10-14 and 18-20 depend directly or indirectly from claim 9. Specifically, claim 10 recites that the kit according to claim 9 further comprises c) the amplification primers SEQ ID NO: 19 and SEQ ID NO: 20 and the probe SEQ ID NO: 30, for detection and quantification of the amount of a human single copy gene (see the specification, page 4, lines 3-5, and Tables 1 and 2 at pages 22 and 23, and see Tables 1 and 2 as amended in the Second Preliminary Amendment filed December 12, 2005 to include SEQ ID NOS). Claim 11 depends from claim 10 and recites that the gene is HUMPBGDA, Homo sapiens hydroxymethylbilane synthase gene, accession no. (accnr) M95623.1 (see the specification, page 4, lines 3-6).

Claims 12, 18 and 19 depend from claims 9, 10 and 11, respectively, and recite that the kit further comprises d) at least two different fluorophores (see the specification, page 4, line 7). Claim 13 depends from claim 10 and recites that the kit further comprises d) three different fluorophores (see the specification, page 4, lines 7-15).

Claims 14 and 20 depend from claims 9 and 11 and recite that the kit is for detection and diagnose of cervical cancer (see the specification, page 4, lines 17-18).

According to independent claim 21, the kit for detection and quantification of HPV comprises a) forward and reverse E7 amplification primers for HPV 16, forward and reverse E1 amplification primers for HPV 18 and 45, and forward and reverse E6 amplification primers for HPV 31, and probes therefore (see the specification, page 2, lines 18-27 and page 10, lines 14-19). The kit of claim 21 optionally comprises b) forward and reverse L1 amplification primers for HPV 33, 52 and 58, forward and reverse E7 amplification primers for HPV 39, and forward and reverse E4 amplification primers for HPV 35, and probes therefore (see the specification, page 2, lines 18-27 and page 10, lines 14-21).

Claims 22-26 depend directly or indirectly from claim 21. Specifically, claim 22 recites the kit of claim 21 further comprises c) forward and reverse amplification primers and a probe therefore, for detection and quantification of the amount of a human single copy gene (see the specification, page 2, line 30-page 3, line 16, page 3, line 26, and page 10, lines 8-9). Claim 23 depends from claim 22 and recites that the gene is HUMPBGDA, Homo sapiens hydroxymethylbilane synthase gene, accnr M95623.1 (see the specification, page 4, lines 3-6).

Claim 24 depends from claim 21 and recites that the kit further comprises d) at least two different fluorophores (see the specification, page 4, line 7), while claim 25 depends from claim 22 and recites that the kit further comprises d) three different fluorophores (see the specification, page 4, lines 7-15).

Finally, claim 26 recites that the kit is for detection and diagnose of cervical cancer (see the specification, page 4, lines 17-18).

VI. GROUNDS OF REJECTION TO BE REVIEWED ON APPEAL

There are four grounds of rejection presented for review on appeal:

A. The rejection of claims 9 and 21 under 35 U.S.C. §103(a) as being unpatentable over the Kroeger et al U.S. Patent Publication No. 2002/0137021 in view of the Gissmann et al U.S. Patent No. 6,228,368, the Goldsborough et al GenBank Accession No. J04353 (1994), Seedorf et al, *EMBO J.*, 6:139-144 (1987), Sastre-Garau et al, *J. Gen. Virol.,* 81:1983-1993 (2000) and GenBank Accession No. AJ242956, and Buck et al, *Biotechniques,* 27:528-536 (1999).

B. The rejection of claims 10, 11, 22 and 23 under 35 U.S.C. §103(a) as being unpatentable over the Kroeger et al U.S. Patent Publication No. 2002/0137021 in view of the Gissmann et al U.S. Patent No. 6,228,368, the Goldsborough et al GenBank Accession No. J04353 (1994), Seedorf et al, *EMBO J.*, 6:139-144 (1987), Sastre-Garau et al, *J. Gen. Virol.,* 81:1983-1993

(2000) and GenBank Accession No. AJ242956, and Buck et al, *Biotechniques,* 27:528-536 (1999), and in further view of Yoo et al, *Genomics*, 15:21-29 (1993) and GenBank Accession No. M95623.

C. The rejection of claims 12, 14, 24 and 26 under 35 U.S.C. §103(a) as being unpatentable over the Kroeger et al U.S. Patent Publication No. 2002/0137021 in view of the Gissmann et al U.S. Patent No. 6,228,368, the Goldsborough et al GenBank Accession No. J04353 (1994), Seedorf et al, *EMBO J.*, 6:139-144 (1987), Sastre-Garau et al, *J. Gen. Virol.,* 81:1983-1993 (2000) and GenBank Accession No. AJ242956, and Buck et al, *Biotechniques,* 27:528-536 (1999), and in further view of Swan et al, *J. Clin. Microbio.*, 35:886-891 (1997).

D. The rejection of claims 13, 18-20 and 25 under 35 U.S.C. §103(a) as being unpatentable over the Kroeger et al U.S. Patent Publication No. 2002/0137021 in view of the Gissmann et al U.S. Patent No. 6,228,368, the Goldsborough et al GenBank Accession No. J04353 (1994), Seedorf et al, *EMBO J.*, 6:139-144 (1987), Sastre-Garau et al, *J. Gen. Virol.,* 81:1983-1993 (2000) and GenBank Accession No. AJ242956, and Buck et al, *Biotechniques,* 27:528-536 (1999), and in further view of Yoo et al, *Genomics*, 15:21-29 (1993) and GenBank Accession No. M95623, and Swan et al, *J. Clin. Microbio.*, 35:886-891 (1997).

VII. ARGUMENTS

As will be set forth in detail below, the kits defined by claims 9-14 and 18-26 are nonobvious over and patentably distinguishable from the respective cited combinations of references on which the rejections under 35 U.S.C. §103(a) set forth above are based. Accordingly, the rejections under 35 U.S.C. §103(a) should be reversed, and favorable action by the Board is respectfully requested.

A. Claims 9 and 21 are Nonobvious

Claims 9 and 21 are nonobvious over the Kroeger et al U.S. Patent Publication No. 2002/0137021 (Kroger) in view of the Gissmann et al U.S. Patent No. 6,228,368 (Gissmann), the

Goldsborough et al GenBank Accession No. J04353 (1994) (Goldsborough), Seedorf et al, *EMBO J.*, 6:139-144 (1987) (Seedorf), Sastre-Garau et al, *J. Gen. Virol.,* 81:1983-1993 (2000) and GenBank Accession No. AJ242956 (Sastre-Garau), and Buck et al, *Biotechniques,* 27:528-536 (1999) (Buck). Accordingly, the rejection of claims 9 and 21 under 35 U.S.C. §103(a) should be reversed.

1. The Examiner's Rejection

In rejecting claims 9 and 21 under 35 U.S.C. §103(a), the Examiner asserted that Kroeger teaches a kit for detecting oncogenic HPV, including HPV 16, 18, 31 and 45, referring to Table 1 on page 2, the kit comprising primers and probes that could be used in a cocktail for amplification and detection of multiple HPV types at once. The Examiner admitted that Kroeger does not teach a kit comprising the amplification primers of SEQ ID NOS: 1-8 and the probes of SEQ ID NOS: 21-24 for detection of HPV 16, 18, 31, and 45, wherein the primers and probes specific for HPV 16 detect a sequence in the E7 open reading frame, the primers and probes specific for HPV 18 and 45 detect a sequence in the E1 open reading frame, and the primers and probes specific for HPV 31 detect a sequence in the E6 open reading frame.

However, the Examiner further asserted it would have been "obvious to try" the sequences taught by Gissmann, Goldsborough, Seedorf and Sastre-Garau to design amplification primers and probes for a kit to detect and quantify HPV in a type-specific manner as taught by Kroeger, relying on *KSR International Co. v. Teleflex, Inc.*, 127 S.Ct. 1727 (2007). The Examiner specifically asserted that:

(a) Gissmann teaches a sequence within the E7 open reading frame of HPV 16 that can be used for designing the claimed primers of SEQ ID NOS: 1 and 2 and probe of SEQ ID NO: 21, the Examiner referring to positions 91-111, 168-146 and 121-142, respectively, of SEQ ID NO: 3 of Gissmann as homologous to the claimed SEQ ID NOS: 1, 2 and 21, respectively;

(b) Goldsborough teaches a sequence within the E6 open reading frame of HPV 31 that can be used for designing the claimed primers of SEQ ID NOS: 3 and 4 and probe of SEQ ID NO: 22, the Examiner referring to positions 476-497, 556-533 and 529-507, respectively of J04353 of Goldsborough as homologous to the claimed SEQ ID NOS: 3, 4 and 22, respectively;

(c) Seedorf teaches a sequence within the E1 open reading frame of HPV 18 that can be used for designing the claimed primers of SEQ ID NOS: 5-7 and probe of SEQ ID NO: 23/SEQ ID NO: 24, the Examiner referring to positions 1093-1113, 1168-1148 and 1115-1140 of Fig. 1a of Seedorf as homologous to the claimed SEQ ID NOS: 5/6, 7 and 23/24, respectively;

(d) Sastre-Garau teaches a sequence within the E1 open reading frame of HPV 45 that can be used for designing the claimed primer of SEQ ID NO: 8, the Examiner referring to positions 7185-7164 of AJ242956 of Sastre-Garau as homologous to the claimed SEQ ID NO: 8.

The Examiner relied on Buck et al as evidencing the equivalence of primers.

2. The Rejection of Claims 9 and 21 Should be Reversed

The kits of claims 9 and 21 are nonobvious over the combination of Kroeger in view of Gissmann, Goldsborough, Seedorf, Sastre-Garau and Buck, whereby the rejection under 35 U.S.C. §103(a) should be reversed.

More particularly, as defined by independent claim 9, the kit for detection and quantification of HPV comprises the amplification primers SEQ ID NO: 1, SEQ ID NO: 2, SEQ ID NO: 3, SEQ ID NO: 4, SEQ ID NO: 5/SEQ ID NO: 6, SEQ ID NO: 7 and SEQ ID NO: 8, and the probes SEQ ID NO: 21, SEQ ID NO: 22 and SEQ ID NO: 23/SEQ ID NO: 24, for HPV 16, 31, 18, and 45. According to independent claim 21, the kit for detection and quantification of HPV comprises forward and reverse E7 amplification primers for HPV 16, forward and reverse E1 amplification primers for HPV 18 and 45, and forward and reverse E6 amplification primers for HPV 31, and probes therefore. Additional specified primers and probes are optionally included in each kit.

As described in the present specification, for example at page 2, beginning at line 24, the kits of the present invention have the advantage of detecting and quantifying the HPV types most commonly detected in cervical tumors, while, importantly, minimizing the number of parallel reactions performed for each sample, therefore making the kits suitable for use in routine screening of cervical swab samples. Further, as described in the specification, for example at page 3, beginning at line 7, the primers and probes are selected so as not to compete during the amplification reaction and detection. Particularly, the Board's attention is directed to the present specification at page 10, beginning at line 14, which discloses that the primers and probes in the claimed kits are selected and combined to optimize the ability for balanced, co-amplification of different HPV types in a mixed sample and to avoid hindrances to an efficient PCR. Specifically, the amplicon for HPV 16 is located in E7, that for HPV 18/45 in E1, and that for HPV 31 in E6. The amplicons for HPV 33, 52 and 58, HPV 39 and HPV 35, when included, are respectively located in L1, E7 and E4. Accordingly, the defined kit optimizes the ability for balanced co-amplification. As described in detail at pages 17-20 of the present application, the kits of claims 9 and 21 make it possible to quantitatively analyze multiple types of HPV, or groups of HPV, in one reaction vessel by providing the claimed combination of primers and probes which do not compete during amplification and detection. The kits of the invention therefore provide a significant advantage in the ability to quantify individual HPV types in mixed infections.

Kroeger discloses probe sequences useful for detecting oncogenic HPV types 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59 and 68 in a test sample (Abstract). Kroeger indicates that all of the probes hybridize within an approximately 140 bp region of the L1 gene found in the HPV genome (paragraph [0007]) and that, while the probes individually can be used to detect the oncogenic HPV type(s) for which they are specific, a cocktail comprising two or more of the oligos can be employed to detect several HPV types at once (paragraph [0007]).

However, Kroeger does not teach or suggest a combination of probes as is employed in the kits of claim 9 or claim 21. Not only does Kroeger fail to disclose or suggest the specific combination of probes and primers recited in claim 9, Kroeger fails to disclose or suggest a kit comprising probes and primers which provide amplification in different HPV reading frames as is provided by claims 9 and 21. In fact, Kroeger teaches away from the combinations of probes and primers as required by claims 9 and 21, and the resulting optimization for balanced co-amplification provided by the kits of the present invention, in that Kroeger specifically requires the use of probes that all hybridize within an approximately 140 bp region of the L1 gene of the HPV genome. Kroeger therefore teaches away from the amplification in different HPV reading frames which is achieved by the present kits. It is error to find obviousness where references diverge from and teach away from the invention at hand, *In re Fine*, 5 U.S.P.Q.2d 1596, 1599 (Fed. Cir. 1988). Thus, Kroeger does not provide a basis for rendering the kits of claims 9 and 21 obvious.

In the final Official Action dated October 27, 2009, the Examiner responded to the above arguments by merely asserting that "Kroeger provides motivation to combine multiple primers and probes in a kit since this reference teaches a kit that not only contains multiple components for amplification, but that such components can be used for simultaneous detection of multiple HPV types" (page 16). As such, the Examiner failed to indicate how one of ordinary skill in the art would be motivated to proceed contrary to the specific advantage espoused by Kroeger, namely using probes that all hybridize in a 140 bp region of the L1 gene of the HPV genome, and rather provide a kit comprising probes and primers which amplify in different HPV reading frames as in the kits defined by claims 9 and 21. Accordingly, a prima facie case of obviousness cannot be established based on Kroeger.

The deficiencies of Kroeger are not resolved by the secondary references. Each of the secondary references cited in the rejections respectively discloses one or more sequences which the

Examiner asserts are "homologous" to one or more specific primers or probes recited in claim 9. However, these references, alone or in combination, fail to teach all of the specific primers of SEQ ID NOS: 1-8 and the specific probes of SEQ ID NOS: 21-24 as required by claim 9. These references also fail to teach a combination of primers and probes having the functionality required by claim 21. Importantly, the cited secondary references further fail to teach a combination of primers and probes that may be employed in a single kit to detect and quantitatively analyze multiple types of HPV, or groups of HPV, in one reaction vessel, without competition among the primers during amplification. In fact, the Examiner's reliance on Buck teaches away from such a combination and demonstrates the nonobviousness of the presently claimed kits as the Examiner asserts that Buck teaches equivalence of all primers. However, Buck is only interested in amplification of a test nucleic acid. On the other hand, the kit of the present invention allows a primer pair to amplify a specific HPV nucleic acid while, at the same time, not amplifying a different but very similar HPV nucleic acid. There is no teaching, suggestion, or motivation in any of the cited references to provide the specific combination of primers recited in claim 9 or claim 21, particularly to obtain this functionality.

More specifically, the Examiner asserted that Gissmann teaches a sequence within the E7 open reading frame of HPV 16 that can be used for designing the claimed primers of SEQ ID NOS: 1 and 2 and the probe of SEQ ID NO: 21 "for the detection and quantification of HPV 16," the Examiner referring to positions 91-111, 168-146 and 121-142, respectively, of SEQ ID NO: 3 of Gissmann as homologous to the claimed SEQ ID NOS: 1, 2 and 21, respectively. However, Gissmann is directed to vaccine formulations and Appellants find no teaching in Gissmann relating to kits for detection and quantification of HPV, or relating to specific primers and probes therefore. Particularly, Appellants find no teaching in Gissmann of the use of a combination of primers that provide amplification in different HPV reading frames as required by claims 9 and 21. Similarly,

Appellants find no teaching in Gissmann that would have motivated one of ordinary skill in the art to proceed contrary to the Kroeger teaching of using multiple probes that all hybridize within a 140 bp region of the L1 gene of the HPV genome and instead to use primers amplifying within the E7 open reading frame of HPV 16.

Finally, the Examiner's reliance on various portions of the 297 bp SEQ ID NO: 3 of Gissmann, identified as the open reading frame of the HPV 16 E7 gene, as exhibiting an unspecified degree of homology to the claimed primers of SEQ ID NOS: 1 and 2 and probe of SEQ ID NO: 21 does not prima facie teach or suggest the specific primers and probe recited in SEQ ID NOS: 1, 2 and 21, respectively, required in the kit of claim 9. Moreover, the 297 bp SEQ ID NO: 3 of Gissmann does not prima facie teach or suggest combinations of primers and probes that do not compete during the amplification reactions and detection phases, an inherent feature of the primers and probes recited in claims 9 and 21. Thus, Gissmann does not resolve any of the deficiencies of Kroeger in rendering the kits of claims 9 and 21 obvious.

The Examiner asserted that Goldsborough teaches a sequence within the E6 open reading frame of HPV 31 that can be used for designing the claimed primers of SEQ ID NOS: 3 and 4 and the probe of SEQ ID NO: 22 "for the detection and quantification of HPV 31", the Examiner referring to positions 476-497, 556-533 and 529-507, respectively of J04353 of Goldsborough as homologous to the claimed SEQ ID NOS: 3, 4 and 22, respectively. However, Goldsborough merely teaches the 7912 bp sequence of the HPV 31 genome DNA. Appellants find no teaching in Goldsborough relating to kits for detection and quantification of HPV, or relating to specific primers and probes therefore. Particularly, Appellants find no teaching in Goldsborough of the use of a combination of primers that provide amplification in different HPV reading frames as required by claims 9 and 21. Similarly, Appellants find no teaching in Goldsborough that would have motivated one of ordinary skill in the art to proceed contrary to the Kroeger teaching of using multiple probes

that all hybridize within a 140 bp region of the L1 gene of the HPV genome and instead to use primers amplifying within the E6 open reading frame of HPV 31.

The Examiner's reliance on various portions of the 7912 bp sequence of Goldsborough, identified as the HPV 31 genome DNA, as exhibiting an unspecified degree of homology to the claimed primers of SEQ ID NOS: 3 and 4 and probe of SEQ ID NO: 22 does not prima facie teach or suggest the specific primers and probe recited in SEQ ID NOS: 3, 4 and 22, respectively, required in the kit of claim 9. Moreover, the 7912 bp sequence of Goldsborough does not prima facie teach or suggest combinations of primers and probes that do not compete during the amplification reactions and detection phases, an inherent feature of the primers and probes recited in claims 9 and 21. Thus, Goldsborough does not resolve any of the deficiencies of Kroeger in rendering the kits of claims 9 and 21 obvious.

The Examiner asserted that Seedorf teaches a sequence within the E1 open reading frame of HPV 18 that can be used for designing the claimed primers of SEQ ID NOS: 5-7 and the probe of SEQ ID NOS: 23 and 24 "for the detection and quantification of HPV 18," the Examiner referring to positions 1093-1113, 1168-1148 and 1115-1140 of Fig. 1(a) of Seedorf as homologous to claimed SEQ ID NOS: 5/6, 7 and 23/24, respectively. However, Seedorf is directed to identification of early proteins of the HPV type 16 and type 18 in cervical carcinoma cells. Appellants find no teaching in Seedorf relating to kits for detection and quantification of HPV, or relating to specific primers and probes therefore. Particularly, Appellants find no teaching in Seedorf of the use of a combination of primers that provide amplification in different HPV reading frames as required by claims 9 and 21. To the contrary, Seedorf indicates that "It has to be shown whether we can identify any of these proteins in HPV 16 or HPV 18 infected tissues" (sentence bridging paves 142-143). Similarly, Appellants find no teaching in Seedorf that would have motivated one of ordinary skill in the art to proceed contrary to the Kroeger teaching of using multiple probes that all hybridize within

a 140 bp region of the L1 gene of the HPV genome and instead to use primers amplifying within the E1 open reading frame of HPV 18.

The Examiner's reliance on various portions of the 1730 bp sequence of the early region of HPV 18 set forth in Fig. 1(a) of Seedorf as exhibiting an unspecified degree of homology to the claimed primers of SEQ ID NOS: 5/6 and 7 and probe of SEQ ID NO: 23/24 does not prima facie teach or suggest the specific primers and probe recited in SEQ ID NOS: 5/6, 7 and 23/24, respectively, required in the kit of claim 9. Moreover, the 1730 bp sequence of the early region of HPV 18 set forth in Fig. 1(a) of Seedorf does not prima facie teach or suggest combinations of primers and probes that do not compete during the amplification reactions and detection phases, an inherent feature of the primers and probes recited in claims 9 and 21. Thus, Seedorf does not resolve any of the deficiencies of Kroeger in rendering the kits of claims 9 and 21 obvious.

The Examiner asserted that Sastre-Garau teaches a sequence within the E1 open reading frame of HPV 45 that can be used for designing the claimed primer of SEQ ID NO: 8 "for the detection and quantification of HPV 45," the Examiner referring to positions 7185-7164 of AJ242956 of Sastre-Garau as homologous to the claimed SEQ ID NO: 8. However, Sastre-Garau is directed to a study of distinct patterns of alteration of *myc* genes associated with integration of human papillomavirus type 16 or type 45 DNA in two genital tumors. The Sastre-Garau GenBank reference discloses the 8039 bp HPV 45 gene sequence. Appellants find no teaching in Sastre-Garau relating to kits for detection and quantification of HPV, or relating to specific primers and probes therefore. Particularly, Appellants find no teaching in Sastre-Garau of the use of a combination of primers that provide amplification in different HPV reading frames as required by claims 9 and 21. Similarly, Appellants find no teaching in Sastre-Garau that would have motivated one of ordinary skill in the art to proceed contrary to the Kroeger teaching of using multiple probes

that all hybridize within a 140 bp region of the L1 gene of the HPV genome and instead to use primers amplifying within the E1 open reading frame of HPV 45.

Finally, the Examiner's reliance on a single 22 bp portion of the 8039 bp HPV 45 gene sequence of Sastre-Garau as exhibiting an unspecified degree of homology to the claimed primer of SEQ ID NO: 8 does not prima facie teach or suggest the specific primer recited in SEQ ID NO: 8, required in the kit of claim 9. Moreover, the 8039 bp sequence of Sastre-Garau does not prima facie teach or suggest combinations of primers and probes that do not compete during the amplification reactions and detection phases, an inherent feature of the primers and probes recited in claims 9 and 21. Thus, Sastre-Garau does not resolve any of the deficiencies of Kroeger in rendering the kits of claims 9 and 21 obvious.

The Examiner relied on the Supreme Court's decision in *KSR International Co. v. Teleflex, Inc.*, *supra,* to assert it would have been obvious to try the asserted combinations of primers and probes. However, in *KSR*, the Supreme Court indicated that the instance in which a combination which is obvious to try might show an invention was obvious under §103 is when there are "a finite number of identified, predictable solutions" to a design need or market pressure, *supra* at 1742. That is not the case with the present combination of references as Kroeger, along with the various secondary references, show there are an almost infinite number of sequences that can be selected from the teachings of the secondary references and an almost infinite number of combinations thereof, with no evidence or expectation that all such sequences achieve the benefits of the present invention and allow detection and quantification of different HPV types without competition in amplification and detection steps.

Additionally, none of the secondary references of Gissmann, Goldsborough, Seedorf or Sastre-Garau are directed to detection and quantification of HPV. Thus, even if the sequences at the various positions noted by the Examiner could be used for detection and quantification, there is no

indication in any of the references or otherwise of record which would have motivated one of ordinary skill in the art to select such sequences and employ them in combination. In determining patentability under 35 U.S.C. §103, it is necessary to determine whether there was an apparent reason to combine the known elements in the fashion of the claim at issue, *KSR International Co. v. Teleflex, Inc.*, *supra* at 1740-41. None of the cited references provide any apparent reason to select from the various teachings of each secondary reference the portions of sequences asserted as relevant by the Examiner and to combine such selected teachings as primers and probes in a single kit as recited in claim 9 or claim 21, particularly to provide the ability to analyze multiple types of HPV, or groups of HPV, in one reaction vessel, without competition among the various primers and probes during amplification and detection.

Apparently recognizing that the cited secondary references do not disclose all of the primers and probes of claim 9, the Examiner asserted that since the claimed primers represent structural homologs of the oligonucleotides taught by Gissmann, Goldsborough, Seedorf and Sastre-Garau, "which are 100% derived from sequences expressly suggested by the prior art of Gissmann, Goldsborough, Seedorf and Sastre-Garau as useful for primers for the detection and quantification of human papillomavirus, and concerning which a biochemist of ordinary skill would attempt to obtain alternate compounds with improved properties, the claimed primers are prima facie obvious over the cited references in the absence of secondary considerations" (page 5). First, contrary to the Examiner's assertions, Appellants find no disclosure in the prior art of Gissmann, Goldsborough, Seedorf and Sastre-Garau of primers useful for the detection and quantification of HPV. Moreover, even if a biochemist of ordinary skill would attempt to obtain alternate compounds with improved properties, there is no apparent reason of record that would cause such a biochemist to arrive at the primers and probes of the sequences as defined in claim 9, particularly by selection from the vast possible combinations of base pairs in the sequences of the secondary references.

The Examiner also asserted that Buck provides evidence of the equivalence of primers and the Examiner concluded that Buck therefore provides evidence that all primers would be expected to function and have a reasonable expectation of success. However, as noted above, Buck only discloses amplification of a single test nucleic acid. On the other hand, the kit of the present invention provides multiple sets of primer pairs and a probe to amplify a respective specific HPV nucleic acid while, at the same time, not amplifying a different but very similar HPV nucleic acid. Buck provides no disclosure in this regard. Moreover, Buck discloses that the results were obtained under optimal sequencing conditions with highly pure template and primer and the new generation of sequencing reagents such as the dichlororhodamine dye terminators. Thus, in the unpredictable art of biotechnology, it cannot be concluded that Buck's findings apply to all primers in all amplification reactions, particularly where, as in claims 9 and 21, multiple primer pairs and probes are provided in a single kit without competition.

In the final Official Action of October 27, 2008, the Examiner asserted that the detection and quantification of different HPV types results not from the kit itself but from the use of the kit components in specific process steps that are not under consideration and any function characteristic of the kit components, such as detecting HPV types in a minimum number of reactions without competition among the reagents to avoid hindrances to an efficient PCR for balanced co-amplification, represents an intended use of the product and does not carry weight for examination of the product claims (pages 14-15). However, in determining the differences between the prior art and the claims, the question under 35 U.S.C. §103 is not whether the differences themselves would have been obvious, but whether the claimed invention as a whole would have been obvious. *Stratoflex, Inc. v. Aeroquip Corp.*, 713 F.2d 1530 (Fed. Cir. 1983). Moreover, in determining whether the invention as a whole would have been obvious under 35 U.S.C. §103, the invention as a whole must first be delineated wherein not only the subject matter which is literally recited in the

claim in question is considered, but also those properties of the subject matter which are inherent in the subject matter and are disclosed in the specification must be considered, MPEP §2141.02. Thus, in considering the patentability of the kits of claims 9 and 21, the properties of the recited combinations of primers and probes, i.e., their ability to detect and quantify HPV 16, 18, 31 and 45 without competition, is properly considered. The Examiner cannot ignore the unobvious advantages provided by the combination of primers and probes as claimed. When these advantages are properly considered, it is apparent that the claimed kits are patentably distinguished from the cited combinations of references.

The Examiner also asserted that one of ordinary skill in the art would be able to design a reasonable number of primer and probe sequences from the sequences taught by the cited references using primer and probe design software available at the time the invention was made that would have a reasonable chance of success of detecting type-specific HPV sequences and based on the teachings of Kroeger, the skilled practitioner would also have been able to combine one or more sets of reagents to arrive at a kit for detecting multiple HPV types. Importantly, however, the Examiner has not provided any evidence of record indicating why one of ordinary skill in the art would use "primer and probe design software available at the time the invention was made" to select primers and probes from the teachings of the secondary references, particularly when Kroeger employs probes which all hybridize to a 140 bp region of the L1 gene. Further, the evidence which is of record does not provide any apparent reason for one of ordinary skill in the art to combine primers and probes as recited in claim 9 or claim 21. Thus, even if such software existed, and one of skill in the art could have used it, there is no reason of record which would have motivated one of ordinary skill in the art to do so, particularly with an expectation of success, namely avoiding competition among primers and probes. The Examiner's reference to the "ability" of one of ordinary skill in the

art does not substitute for the motivation and expectation of success necessary for finding an invention obvious.

Accordingly, the kits defined by claims 9 and 21 are nonobvious over and patentably distinguishable from the combination of Kroeger in view of Gissmann, Goldsborough, Seedorf, Sastre-Garau and Buck. Hence, the rejection of claims 9 and 21 under 35 U.S.C. §103(a) should be reversed.

B. Claims 10, 11, 22 and 23 are Not Obvious

Claims 10, 11, 22 and 23 are nonobvious over and patentably distinguishable from the combination of Kroeger in view of Gissmann, Goldsborough, Seedorf, Sastre-Garau and Buck, and further in view of Yoo et al, *Genomics*, 15:21-29 (1993) and GenBank Accession No. M95623 (Yoo). Therefore, the rejection of these claims under 35 U.S.C. §103(a) should be reversed.

1. The Examiner's Rejection

In rejecting claims 10, 11, 22 and 23 under 35 U.S.C. §103(a), the Examiner relied on Kroeger, Gissmann, Goldsborough, Seedorf, Sastre-Garau and Buck for the reasons set forth in the rejection of claims 9 and 21 discussed in the preceding section VII.A. The Examiner admitted that these references do not teach the claimed amplification primers of SEQ ID NO: 19 and SEQ ID NO: 20 and probe of SEQ ID NO: 30 for detection and quantification of the amount of the human single copy gene hydroxymethylbilane synthase (HUMPBGDA). The Examiner asserted however that Yoo teaches a sequence that can be used for designing the claimed primers and probe of SEQ ID NOS: 19, 20 and 30 for detection and quantification of the human single copy gene HUMPBGDA, the Examiner referring to positions 4750-4770, 4868-4850 and 4788-4813, respectively, of the PBGD sequence of Yoo as homologous to the claimed SEQ ID NOS: 19, 20 and 30, respectively.

2. The Rejection of Claims 10, 11, 22 and 23 Should be Reversed

The kits of claims 10, 11, 22 and 23 are nonobvious over and patentably distinguishable from the combination of Kroeger in view of Gissmann, Goldsborough, Seedorf, Sastre-Garau, Buck, and Yoo, whereby the rejection under 35 U.S.C. §103(a) should be reversed.

Claims 10 and 22 depend from claims 9 and 21, respectively, and recite that the kit further comprises primers and a probe for detection and quantification of the amount of a human single copy gene. According to claim 10, the amplification primers are SEQ ID NO: 19 and SEQ ID NO: 20 and the probe is SEQ ID NO: 30, while claim 22 recites the amplification primers as forward and reverse primers. Claims 11 and 23 depend from claims 10 and 22, respectively, and recite that the gene is HUMPBGDA, Homo sapiens hydroxymethylbilane synthase gene, accnr M95623.1.

The kits of claims 9 and 21, from which claims 10, 11, 22 and 23 directly or indirectly depend, are discussed in detail above, as are the deficiencies of Kroeger, Gissmann, Goldsborough, Seedorf, Sastre-Garau, and Buck which prevent the cited combination of references from rendering the kits of claims 9 and 21 obvious. Those discussions are incorporated herein and equally demonstrate deficiencies in the rejection of claims 10, 11, 22 and 23 under 35 U.S.C. §103(a). Moreover, the deficiencies of Kroeger, Gissmann, Goldsborough, Seedorf, Sastre-Garau, and Buck which prevent the cited combination of references from rendering the kits of claims 10, 11, 22 and 23 obvious are not resolved by Yoo.

The Examiner asserted that Yoo teaches a sequence that can be used for designing primers and a probe of SEQ ID NOS: 19, 20 and 30 for detection and quantification of the human single copy gene HUMPBGDA, the Examiner referring to positions 4750-4770, 4868-4850 and 4788-4813, respectively, of the PBGD sequence of Yoo as homologous to the claimed SEQ ID NOS: 19, 20 and 30, respectively. However, Yoo is directed to a study of amplifiable polymorphisms in the human gene hydroxymethylbilane synthase (HMB-synthase) gene, and the Yoo GenBank reference

discloses the 10024 bp HUMPBGDA 45 gene sequence. Appellants find no teaching in Yoo relating to kits for detection and quantification of HPV, or relating to specific primers and probes contained in such a kit. Particularly, Appellants find no teaching in Yoo of the combination of primers and a probe for detection and quantification of the amount of a human single copy gene in such a kit, or recognition that such a combination may be useful to normalize HPV detection results obtained with the combinations of other primers and probes contained in such a kit. That a human single copy gene is known according to Yoo does not render primers and a probe therefore obvious for inclusion in the kits of the present claims further containing specified primers and probes for measuring individual HPV types. Finally, the Examiner's reliance on three 19-25 bp portions of the 10024 bp HUMPBGDA gene sequence of Yoo as exhibiting an unspecified degree of homology to the primers and probe of SEQ ID NOS: 19, 20 and 30, respectively, does not prima facie teach the specific primers and probe recited in SEQ ID NOS: 19, 20 and 30 required in the kit of claims 10 and 11. Moreover, the 10024 bp sequence of Yoo does not prima facie teach providing primers and a probe therefore in a kit for detection and quantification of HPV as required in the kits of claims 22 and 23.

The Examiner again relied on the Supreme Court's decision in *KSR International Co. v. Teleflex, Inc.*, *supra,* to assert it would have been obvious to try the primers and probes required by claims 10, 11, 22 and 23. However, as noted above, the instance in which a combination which is obvious to try might show an invention was obvious under §103 is when there are "a finite number of identified, predictable solutions" to a design need or market pressure, *supra* at 1742. The Examiner has not shown that, in the present case, there are only a finite number of identified, predictable solutions for achieving normalization to render obvious claims 10, 11, 22 and 23. In fact, at least with respect to claim 10, reciting the inclusion of primers of SEQ ID NOS: 19 and 20 and a probe of SEQ ID NO: 30, the mere size of the 10024 bp sequence of Yoo does not indicate

that there are only a finite number of primers or probes thereof. Thus, Yoo does not resolve any of the deficiencies of Kroeger, Gissmann, Goldsborough, Seedorf, Sastre-Garau, and Buck and does not, in combination therewith, render the kits of claims 10, 11, 22 and 23 obvious.

Accordingly, the kits defined by claims 10, 11, 22 and 23 are nonobvious over and patentably distinguishable from the combination of Kroeger in view of Gissmann, Goldsborough, Seedorf, Sastre-Garau, Buck and Yoo. Hence, the rejection of claims 10, 11, 22 and 23 under 35 U.S.C. §103(a) should be reversed.

C. Claims 12, 14, 24 and 26 are Not Obvious

Claims 12, 14, 24 and 26 are nonobvious over and patentably distinguishable from the combination of Kroeger in view of Gissmann, Goldsborough, Seedorf, Sastre-Garau and Buck, and further in view of Swan et al, *J. Clin. Microbio.*, 35:886-891 (1997) (Swan). Therefore, the rejection of these claims under 35 U.S.C. §103(a) should be reversed.

1. The Examiner's Rejection

In rejecting claims 12, 14, 24 and 26 under 35 U.S.C. §103(a), the Examiner relied on Kroeger, Gissmann, Goldsborough, Seedorf, Sastre-Garau and Buck for the reasons set forth in the rejection of claims 9 and 21 discussed in the preceding section VII.A. The Examiner admitted that these references do not teach a kit comprising at least two different fluorophores for detection and diagnosis of cervical cancer. The Examiner asserted however that Swan teaches a type-specific fluorogenic probe assay for detection and quantification of HPV, including high-risk types associated with cervical cancer, using probes containing FAM or HEX and a rhodamine quencher dye, TAMRA. The Examiner concluded it would have been obvious to combine the teachings of Kroeger, Gissmann, Goldsborough, Seedorf, Sastre-Garau and Buck with those of Swan since the probes can all be readily prepared with fluorescent labels during synthesis using the necessary phoshoramidites and esters and an ordinary practitioner would have been motivated to use HPV

sequences in order to design primers and fluorescently-labeled probes to provide a kit for performing a fast, simple and highly sensitive detection method for typing HPV DNA.

2. The Rejection of Claims 12, 14, 24 and 26 Should be Reversed

The kits of claims 12, 14, 24 and 26 are nonobvious over and patentably distinguishable from the combination of Kroeger, Gissmann, Goldsborough, Seedorf, Sastre-Garau, Buck, and Swan, whereby the rejection under 35 U.S.C. §103(a) should be reversed.

Claims 12 and 24 depend from claims 9 and 21, respectively, and recite that the kits further comprise at least two different fluorophores. Claims 14 and 26 depend from claims 9 and 21, respectively, and recite that the kits are for detection and diagnose of cervical cancer.

The kits of claims 9 and 21, from which claims 12, 14, 24 and 26 directly depend, are discussed in detail above, as are the deficiencies of Kroeger, Gissmann, Goldsborough, Seedorf, Sastre-Garau, and Buck which prevent the cited combination of references from rendering the kits of claims 9 and 21 obvious. Those discussions are incorporated herein and equally demonstrate deficiencies in the rejection of claims 12, 14, 24 and 26 under 35 U.S.C. §103(a). Moreover, the deficiencies of Kroeger, Gissmann, Goldsborough, Seedorf, Sastre-Garau, and Buck which prevent the cited combination of references from rendering the kits of claims 12, 14, 24 and 26 obvious are not resolved by Swan.

More particularly, Swan discloses the preparation and use of probes in a fluorogenic probe assay for detection of HPV. Swan's probes however were all directed at the L1 region of the cervical cancer-associated HPV types 16, 18, 31, 33 and 35. Swan acknowledges that the probes disclosed therein exhibit cross reactivity, wherein, for example, a signal equivalent to between 30 and 100 copies of HPV-33 was seen with 2000 copies of HPV-16 or HPV-51. In contrast, in the kits of claims 9 and 21, from which claims 12, 14, 24 and 26 depend, the primers and probes therefore are directed to different HPV reading frames. As a result, competition in both

amplification and detection using the claimed probes and primers is avoided. Not only does Swan fail to resolve the deficiencies of Kroeger, Gissmann, Goldsborough, Seedorf, Sastre-Garau, and Buck, the indicated cross-reactivity of the Swan system further demonstrates disadvantages of the Kroeger system, wherein all of the probes hybridize within an approximately 140 bp region of the L1 gene. Thus, notwithstanding any use by Swan of at least two different fluorophores, Swan fails, in combination with Kroeger, Gissmann, Goldsborough, Seedorf, Sastre-Garau, and Buck, to render the kits of claims 12, 14, 24 and 26 obvious.

Accordingly, the kits defined by claims 12, 14, 24 and 26 are nonobvious over and patentably distinguishable from the combination of Kroeger in view of Gissmann, Goldsborough, Seedorf, Sastre-Garau, Buck and Swan. Hence, the rejection of claims 12, 14, 24 and 26 under 35 U.S.C. §103(a) should be reversed.

D. Claims 13, 18-20 and 25 are Not Obvious

Claims 13, 18-20 and 25 are nonobvious over and patentably distinguishable from the combination of Gissmann, Goldsborough, Seedorf, Sastre-Garau, Buck, Yoo and Swan, and, therefore, the rejection of these claims under 35 U.S.C. §103(a) should be reversed.

1. The Examiner's Rejection

In rejecting claims 13, 18-20 and 25 under 35 U.S.C. §103(a), the Examiner relied on Kroeger, Gissmann, Goldsborough, Seedorf, Sastre-Garau, Buck and Yoo for the reasons set forth in the rejection of claims 10, 11, 22 and 23 set forth in the preceding section VII.B. The Examiner admitted that these references do not teach a kit comprising three different fluorophores for detection and diagnosis of cervical cancer. The Examiner asserted however that Swan teaches a type-specific fluorogenic probe assay for detection and quantification of HPV, including high-risk types associated with cervical cancer, using probes containing FAM or HEX and a rhodamine quencher dye, TAMRA. The Examiner concluded it would have been obvious to combine the

teachings of Kroeger, Gissmann, Goldsborough, Seedorf, Sastre-Garau, Buck and Yoo with those of Swan since the probes can all be readily prepared with fluorescent labels during synthesis using the necessary phoshoramidites and esters and an ordinary practitioner would have been motivated to use HPV and PBGD probes in order to design primers and fluorescently-labeled probes to provide a kit for performing a fast, simple and highly sensitive detection method for typing HPV DNA.

2. The Rejection of Claims 13, 18-20 and 25 Should be Reversed

The kits of claims 13, 18-20 and 25 are nonobvious over and patentably distinguishable from the combination of Kroeger, Gissmann, Goldsborough, Seedorf, Sastre-Garau, Buck, Yoo and Swan, whereby the rejection under 35 U.S.C. §103(a) should be reversed.

Claims 13 and 25 depend from claims 10 and 22, respectively, and recite that the kits further comprise three different fluorophores, while claims 18 and 19 depend from claims 10 and 11, respectively, and recite that the kits further comprise at least two different fluorophores. Claim 20 depends from claim 11 and recites that the kit is for detection and diagnose of cervical cancer. Claims 10 and 11, as noted above, depend directly or indirectly from claim 9 while claim 22 depends from claim 21.

The kits of claims 9 and 21, from which claims 13, 18-20 and 25 indirectly depend, are discussed in detail above, as are the deficiencies of Kroeger, Gissmann, Goldsborough, Seedorf, Sastre-Garau, Buck and Yoo which prevent the cited combination of references from rendering the kits of claims 9 and 21 obvious and in rendering the kits of claims 10, 11 and 22 obvious. Those discussions are incorporated herein and equally demonstrate deficiencies in the rejection of claims 13, 18-20 and 25 under 35 U.S.C. §103(a). Moreover, the deficiencies of Kroeger, Gissmann, Goldsborough, Seedorf, Sastre-Garau, Buck and Yoo which prevent the cited combination of references from rendering the kits of claims 13, 18-20 and 25 obvious are not resolved by Swan.

More particularly, Swan discloses the preparation and use of probes in a fluorogenic probe assay for detection of HPV. However, as noted above, Swan's probes were all directed at the L1 region of the cervical cancer-associated HPV types 16, 18, 31, 33 and 35. Swan acknowledges that the probes disclosed therein exhibit cross reactivity, wherein, for example, a signal equivalent to between 30 and 100 copies of HPV-33 was seen with 2000 copies of HPV-16 or HPV-51. In contrast, in the kits of claims 9 and 21, from which claims 13, 18-20 and 25 indirectly depend, the primers and probes therefore are directed to different HPV reading frames. As a result, competition in both amplification and detection using the claimed probes and primers is avoided. Not only does Swan fail to resolve the deficiencies of Kroeger, Gissmann, Goldsborough, Seedorf, Sastre-Garau, Buck, and Yoo, the indicated cross-reactivity of the Swan system further demonstrates disadvantages of the Kroeger system, wherein all of the probes hybridize within an approximately 140 bp region of the L1 gene. Thus, notwithstanding any use by Swan of at least two different fluorophores, Swan fails, in combination with Kroeger, Gissmann, Goldsborough, Seedorf, Sastre-Garau, Buck, and Yoo to render the kits of claims 13, 18-20 and 25 obvious.

Accordingly, the kits defined by claims 13, 18-20 and 25 are nonobvious over and patentably distinguishable from the combination of Kroeger in view of Gissmann, Goldsborough, Seedorf, Sastre-Garau, Buck, Yoo and Swan. Hence, the rejection of claims 13, 18-20 and 25 under 35 U.S.C. §103(a) should be reversed.

VIII. CONCLUSIONS

For the reasons set for the in detail above, the kits defined by claims 9-14 and 18-26 are nonobvious over and patentably distinguishable from the combinations of a) Kroeger in view of Gissmann, Goldsborough, Seedorf, Sastre-Garau, and Buck, b) Kroeger in view of Gissmann, Goldsborough, Seedorf, Sastre-Garau, Buck, and Yoo, c) Kroeger in view of Gissmann, Goldsborough, Seedorf, Sastre-Garau, Buck, and Swan, and d) Kroeger in view of Gissmann,

Goldsborough, Seedorf, Sastre-Garau, Buck, Yoo and Swan. Accordingly, the rejections under 35 U.S.C. §103(a) should be reversed. Favorable action by the Board is respectfully requested.

Please charge the government fee of $540.00 required for filing the present Appeal Brief to Deposit Account 503915.

Respectfully submitted,

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CLAIMS APPENDIX

9. A kit for detection and quantification of human papillomavirus, comprising a) the amplification primers SEQ ID NO: 1, SEQ ID NO: 2, SEQ ID NO: 3, SEQ ID NO: 4, SEQ ID NO: 5/SEQ ID NO: 6, SEQ ID NO: 7 and SEQ ID NO: 8, and the probes SEQ ID NO: 21, SEQ ID NO: 22 and SEQ ID NO: 23/SEQ ID NO: 24, for HPV 16, 31, 18, 45; and optionally b) the amplification primers SEQ ID NO: 9, SEQ ID NO: 10, SEQ ID NO: 11, SEQ ID NO: 12, SEQ ID NO: 13/SEQ ID NO: 14, SEQ ID NO: 15, SEQ ID NO: 16 and SEQ ID NO: 17/SEQ ID NO: 18 and the probes SEQ ID NO: 25, SEQ ID NO: 26 and SEQ ID NO: 27/SEQ ID NO: 28/SEQ ID NO: 29 for HPV 33, 35, 39, 52, and 58.

10. A kit according to claim 9, further comprising c) the amplification primers SEQ ID NO: 19 and SEQ ID NO: 20 and the probe SEQ ID NO: 30, for detection and quantification of the amount of a human single copy gene.

11. A kit according to claim 10, wherein the gene is HUMPBGDA, Homo sapiens hydroxymethylbilane synthase gene, accnr M95623.1.

12. A kit according to claim 9, further comprising d) at least two different fluorophores.

13. A kit according to claim 10, further comprising d) three different fluorophores.

14. A kit according to claim 9 for detection and diagnose of cervical cancer.

18. A kit according to claim 10, further comprising d) at least two different fluorophores.

19. A kit according to claim 11, further comprising d) at least two different fluorophores.

20. A kit according to claim 11 for detection and diagnose of cervical cancer.

21. A kit for detection and quantification of human papillomavirus, comprising a) forward and reverse E7 amplification primers for HPV 16, forward and reverse E1 amplification primers for HPV 18 and 45, and forward and reverse E6 amplification primers for HPV 31, and probes therefore; and optionally b) forward and reverse L1 amplification primers for HPV 33, 52 and 58, forward and reverse E7 amplification primers for HPV 39, and forward and reverse E4 amplification primers for HPV 35, and probes therefore.

22. A kit according to claim 21, further comprising c) forward and reverse amplification primers and a probe therefore, for detection and quantification of the amount of a human single copy gene.

23. A kit according to claim 22, wherein the gene is HUMPBGDA, Homo sapiens hydroxymethylbilane synthase gene, accnr M95623.1.

24. A kit according to claim 21, further comprising d) at least two different fluorophores.

25. A kit according to claim 22, further comprising d) three different fluorophores.

26. A kit according to claim 21 for detection and diagnose of cervical cancer.

EVIDENCE APPENDIX

There is no evidence submitted with the present Appeal Brief.

RELATED PROCEEDINGS APPENDIX

There are no decisions from any related proceedings as described in Section II of the present Appeal Brief.